



Leptomeningeal Spread in Glioblastoma: Diagnostic and Therapeutic Challenges

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Key Words. Glioblastoma • Leptomeningeal spread • Diagnostic • Treatment

ABSTRACT

Background. Glioblastoma (GBM) is the most common and aggressive primary malignant brain tumor. Leptomeningeal spread (LMS) is a severe complication of GBM, raising diagnostic and therapeutic challenges in clinical routine.

Methods. We performed a review of the literature focused on LMS in GBM. MEDLINE and EMBASE databases were queried from 1989 to 2019 for articles describing diagnosis and therapeutic options in GBM LMS, as well as risk factors and pathogenic mechanisms.

Results. We retrieved 155 articles, including retrospective series, case reports, and early phase clinical trials, as well as preclinical studies. These articles confirmed that LMS in GBM remains (a) a diagnostic challenge with cytological proof of LMS obtained in only 35% of cases and (b) a therapeutic challenge with a median overall survival below 2 months with best supportive care alone. For patients faced

with suggestive clinical symptoms, whole neuroaxis magnetic resonance imaging and cerebrospinal fluid analysis are both recommended. Liquid biopsies are under investigation and may help prompt a reliable diagnosis. Based on the literature, a multimodal and personalized therapeutic approach of LMS, including surgery, radiotherapy, systemic cytotoxic chemotherapy, and intrathecal chemotherapies, may provide benefits to selected patients. Interestingly, molecular targeted therapies appear promising in case of actionable molecular target and should be considered.

Conclusion. As the prognosis of glioblastoma is improving over time, LMS becomes a more common complication. Our review highlights the need for translational studies and clinical trials dedicated to this challenging condition in order to improve diagnostic and therapeutic strategies. *The Oncologist* 2020;25:e1763–e1776

Implications for Practice: This review summarizes the diagnostic tools and applied treatments for leptomeningeal spread, a complication of glioblastoma, as well as their outcomes. The importance of exhaustive molecular testing for molecular targeted therapies is discussed. New diagnostic and therapeutic strategies are outlined, and the need for translational studies and clinical trials dedicated to this challenging condition is highlighted.

INTRODUCTION

Glioblastoma (GBM) is the most common and the most aggressive primary malignant brain tumor in adults [1–3]. Its annual incidence is close to 3 per 100,000 persons per year.

The treatment of patients newly diagnosed with GBM relies on maximal safe surgical resection followed by radiotherapy with concurrent and adjuvant temozolomide chemotherapy

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[4]. Despite the intensive therapeutic regimen, the prognosis of patients with GBM remains poor with a median overall survival below 18 months and a 5-year survival rate of 5.6% [2].

The propensity of GBM to metastasize to cerebrospinal fluid (CSF) flow stream, inducing GBM leptomeningeal spread (LMS), was first described in 1931 [5]. LMS results from spreading of tumor cells from brain parenchyma to leptomeninges and CSF and is one of the most severe complications of GBM. Other severe complications of GBM include (a) intratumor hemorrhage, (b) status epilepticus, and (c) hydrocephalus. As the prognosis of patients with GBM improves, LMS becomes a more frequent clinical issue in neuro-oncology [1, 6, 7].

Considered initially a rare complication in gliomas [8], the incidence of LMS seems above the estimated rate of 4%, reaching 25% on postmortem neuropathological studies [1, 5, 6, 9, 10]. In cases of LMS, the median overall survival of patients with GBM varies between 2 and 5 months [1, 6, 7, 11, 12]. No risk factor has been clearly demonstrated, although multiple factors have been suggested: (a) age, (b) histologic features, (c) molecular alterations, (d) anatomical tumor site, and (e) therapeutic interventions (e.g., surgical opening of the ventricles or antiangiogenic therapies) [1, 6, 13–16].

Diagnosis of LMS in patients with GBM is challenging. The sensitivity of classic diagnostic investigations (i.e., magnetic resonance imaging [MRI] and cytological CSF analysis) remains low, failing to identify tumor CSF spread most of the time [17, 18].

There is no standard of care treatment for LMS in patients with GBM, although multiple groups have proposed several therapeutic options (e.g., methotrexate, cytarabine, thiopeta, and/or nimustine) with limited efficacy so far [1, 6, 7, 11, 15, 19–21]. Interestingly, treatment with intrathecal chimeric antigen receptor T cells has demonstrated dramatic efficacy in a single patient [22]. The advent of molecular targeted therapies and immunotherapies supports further exploration of the molecular landscape of CSF-circulating GBM cells [23–26].

Diagnostic and therapeutic challenges raised by LMS in patients with GBM will be presented and discussed in the current review.

MATERIALS AND METHODS

We conducted a survey, from January 1, 1989, to December 31, 2019, in the PubMed database and Scopus-EMBASE using the following combination of terms connected by Boolean operators: (glioma OR high grade glioma OR glioblastoma) AND (meningeal OR leptomeningeal OR leptomeningeal dissemination OR meningeal gliomatosis OR leptomeningeal gliomatosis OR meningeal metastasis OR CSF dissemination) to identify relevant studies related to LMS and glioma.

Our search retrieved 2,043 articles. We excluded (a) duplicate articles, (b) articles in languages other than English and French, and (c) irrelevant articles (i.e., primary meningeal gliomatosis, pediatric tumors). Eighty-five full-text articles were selected. Based on this first selection and linked list of references, additional articles were identified and included in our review. Overall, 155 articles were identified as relevant to the topic. The research algorithm is schematized in Figure 1.

EPIDEMIOLOGY

LMS in high-grade gliomas was reported by several authors (Table 1). In a series of 600 patients with GBM, Vertosick et al. estimated the incidence rate of symptomatic LMS at 2% [1, 6, 7, 10, 11, 27–32]. This incidence rate is probably underestimated because of undiagnosed and asymptomatic cases. Indeed, in autopsy studies, LMS was identified in up to 25% of patients with high-grade glioma [1, 10, 15, 27, 28, 33].

PATHOGENESIS

Little is known about the pathogenesis of LMS. CSF dissemination seems to follow two patterns: (a) intense CSF seeding with limited tumor progression at initial tumor site or (b) minimal CSF seeding with massive tumor progression at initial location [1, 5, 10, 34].

GBM cells migrate from the initial tumor site along brain vessels to subpial, subarachnoid, and subependymal spaces (Fig. 2A) [5, 10, 35, 36]. The leptomeningeal seeding from cortical areas is preceded by subpial spread as an intermediary step [5, 10, 17, 35]. During this migratory process, GBM cells secrete multiple proteases degrading the extracellular matrix (e.g., MMP-1, -2, -7, -9, -14, and -19 with a critical role of MMP-2 and -9) to create a moving space [37–42] and express multiple adhesion-migration proteins (e.g., glycosylated chondroitin sulfate proteoglycans, fibronectin, fascin, and integrins) [35, 39, 41, 43]. Both molecule classes, working synergistically with cytoskeleton, allow tumor cell migration toward leptomeninges and CSF [5, 18, 28, 30, 35, 39, 41, 43–45].

Furthermore, in a mouse model, prolonged vascular endothelial growth factor (VEGF) inhibition converted tumor cell phenotype to invasive/mesenchymal, leading to tumor invasion through perivascular and subpial spaces [46]. Multiple proteins, including FGF, IGFBP2, MMP-2, Podoplanin, fascin, MET, TGF- β , and IL8, are involved in this process, but further insight is needed [44, 46–50].

The role of the glioma stem cell like cells and their cross talk with microenvironment cells in tumor cell migration remains poorly understood [41, 45]. Translational and pre-clinical research are shedding light on molecular and cellular mechanisms of this phenomenon and its implication in invasiveness potential of GBM and in LMS development [26, 37, 51–53].

CLINICAL PRESENTATION

Two thirds of patients with GBM develop LMS within the first 2 years after diagnosis [1, 7, 11, 20, 28, 30, 33, 54]. The median delay from initial diagnosis of GBM to clinicoradiological evidence of LMS varies from 5 to 16.4 months [1, 5–7, 10, 11, 15, 20, 28, 30, 33, 55–58]. This delay is shorter in specific tumor locations, including pineal, spinal, periventricular, and infratentorial [12, 15, 59–66].

Clinical presentation of LMS is heterogeneous, from asymptomatic to severely symptomatic disease [1, 6, 11, 12, 15, 29, 31, 67]. Usually the onset and the worsening of symptoms are progressive; acute presentation is exceptional [5, 12, 27, 36, 68–70].

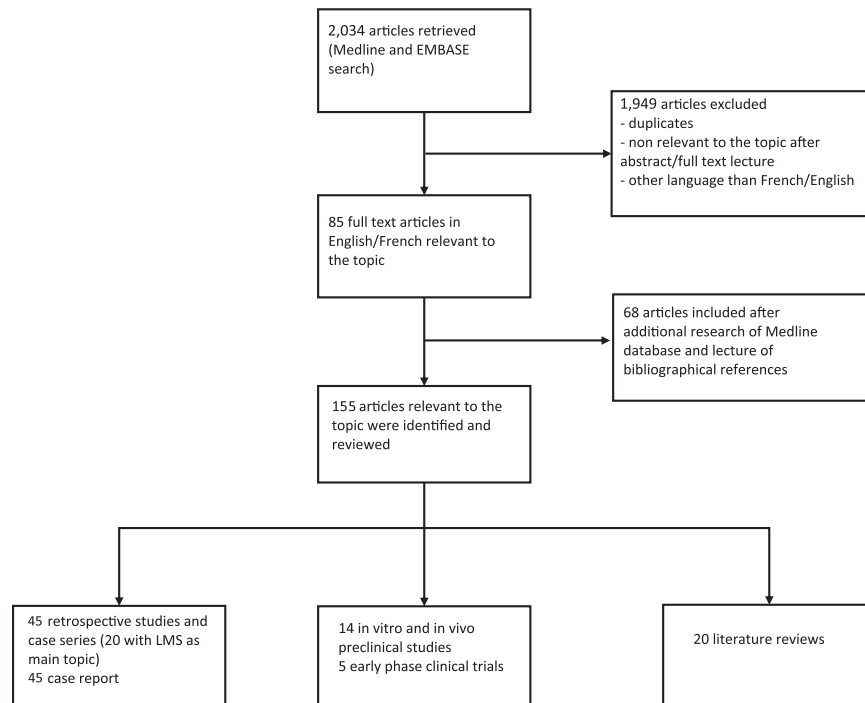


Figure 1. Literature research flow chart showing the selection of publications used in the review.
Abbreviation: LMS, leptomeningeal spread.

Patients with LMS can suffer from cranial nerve palsies, increased intracranial pressure syndrome, hydrocephalus, meningism, and/or focal neurological deficits [1, 7, 15, 20, 33, 71–76]. Seizure frequency does not seem to increase during LMS development [77]. Confusion and generalized cognitive decline are the most common features of LMS in elderly patients with GBM [15, 78, 79]. Although rare, aseptic fever, central neurogenic hyperventilation, and cardiac arrest are reported [5, 11, 12, 70, 80].

Intractable vomiting may be an early symptom of CSF seeding to the fourth ventricle [81]. Cranial nerve deficits, including of the second, third, fourth, sixth, and/or seventh, are observed in 6% of cases [8, 78]. The fourth and seventh cranial nerves are the most frequently involved [78, 82]. Once installed, cranial nerve palsies are often irreversible [5, 27].

Progressive paraplegia [9, 27, 36, 69, 73, 83, 84], sphincter incontinence [1, 11, 36, 55, 80, 84], and spinal ataxia [20, 29, 80] were described when the spinal cord or cauda equina are involved [9, 29, 30, 33, 69, 73, 85, 86]. Isolated symptoms such as paresthesia, ataxia, back pain, and leg or shoulder pain are rare [27, 29, 87, 88]. Radicular pain has been described with various topography: the upper limbs, interscapular [89], thoracic, or lumbar level as well as sciatalgia [1, 5, 11, 15, 20, 33, 55, 90].

Of note, although LMS may manifest as communicating hydrocephalus [33], only 25%–40% of patients with LMS present this complication [75, 91].

RISK FACTORS

A number of risk factors of LMS have been investigated in patients with GBM. Young age (around 35–45 years), brain

location, male gender, long survival after initial diagnosis, and tumor volume seem to be associated with a greater risk of LMS in patients with GBM [1, 6, 27, 78].

The initial tumor location seems to be of importance. Indeed, infratentorial location (in 45%–100% of cases) [1, 5, 10, 13, 62, 63] and GBM of the pineal region [59] are associated with a higher frequency of LMS. The spatial proximity to ventricles and the tumor size were considered as risk factor of LMS, but existing data are conflicting [1, 6, 7, 11]. Indeed, invasive behavior of tumor cells and the environment of the subventricular zone have been pinpointed [1, 14, 15, 30, 85, 92, 93].

Ventricular opening during surgery and repeated surgeries, even more in patients treated with radiotherapy or chemotherapy [5, 89], have been proposed as risk factors of LMS [15, 65, 94, 95]. However, none has been clearly validated [1, 14, 29, 75, 92–97], and prophylactic radiotherapy in these cases does not bring supplementary benefit [98]. Persistence of preoperative leptomeningeal enhancement after initial surgical resection was also correlated with a higher LMS incidence in recurrence [99].

Hydrocephalus with subsequent ependymal fissuring has also been suggested as a potential but not formally validated risk factor [89, 100].

Histological and molecular characteristics of initial tumor were also investigated. Astrocytic phenotype, high Ki67/Mib1 expression index [1, 29, 60, 85, 101, 102], and GFAP loss of expression either at initial diagnosis [10] or at recurrence [28, 29] were correlated with higher risk of LMS. Epithelioid GBM [26, 103, 104] and GBM with a neuronal component or primitive neuroectodermal tumor-like GBM [56, 74] disseminate more frequently to CSF.

Table 1. Leptomeningeal spread in glioblastoma: Retrospective studies and case series

Study	n	Mean age, years	Histology	Status of primary at time of LMS presentation	Latency, mean, months	Mean KPS	LMS treatment	Mean OS after LMS diagnosis, months
Mandel et al. 2014 [1]	36	45	GBM		4.9–12	<70 (34%)	Focal RT, surgery, CT, CT + RT	2.2–4.7
Noh et al. 2015 [6]	75	47	GBM	NA	12	60	RT CT-TMZ, OT-GKS, i.t. MTX	3–6.6
Autran et al. 2019 [7]	31	45	20 GBM, 10 LGG	NA	8	<70 (71%)	BCNU-TMZ ± Beva	5.7 combo 0.6 with palliative care
Onda et al. 1989 [10]	14	53	11 GBM, 3 AG	PD	NA	NA	NA	NA after LMS diagnosis
Andersen et al. 2019 [11]	128	58	GBM	NA	11	70	RT, CT, antiangiogenic Targeted Palliative care	3.2 1.6–7.6 1.6 with palliative care
Bae et al. 2011 [15]	7	50	GBM	PD	12	55 40–80	i.t. MTX, palliative care	2.3
Burger et al. 2016 [55]	9	46	4 GBM, 5 AG	PD	17	70	IFXRT + CT (Iri/CCNU) + Beva	3.8
Pradat et al. 1999 [20]	20	51	8 GBM	PD 41%	9.5	65	Spinal RT, i.v. Thio-PCB, Thio-5FU-VP16-CCNU i.t. MTX/ Thio	3 0.2–10.5
Vertosick et al. 1990 [27]	11	39	GBM	PD	14.1	NA	RT, Surgery	2.8
Arita et al. 1994 [28]	22	31	10 GBM, 11 AA	PD 64%	22	NA	RT, CT (i.t./i.v.), RT-CT	6.5
Dardis et al. 2014 [30]	34	50	24 GBM, 10 AA	PD 57%	7.9	70	RT, CT, i.t. (Depocyt/ MTX)	3.7–9.9
Delattre et al. 1989 [33]	5	31	3 GBM, 2 AA	PD 33%	8.6	NA	Spinal RT, CT CBDCA, i.t. IFN	5.3
Chamberlain et al. 2003 [57]	18	38	8 GBM, 10 AA	PD 70%	5.6	60	RT, systemic CT, MTX i.t.	3
Witham et al. 1999 [58]	14	42	9 GBM, 5 AA	NA	7.7	NA	RT, systemic CT (BCNU): Thiotepa i.t.	10.1
Amitendu et al. 2012 [83]	4	53	3 GBM	NA	7.1	NA	RT, surgery	4
Saito et al. 2003 [86]	11	47	5 GBM, 6 AA	PD	12.7	80	RT, CT, MTX i.t.	8
Karaca et al. 2006 [87]	3	37	GBM	NA	10	NA	Spinal RT, Adjuvant CT	4
Roelz et al. 2015 [94]	27	56	22 GBM, 5 AG	PD 78%	12.1	NA	RT, Surgery, Chemotherapy, RT and CT	7.9

Abbreviations: 5FU, fluorouracil; AA, anaplastic astrocytoma; AG, anaplastic glioma; BCNU, carmustine; Beva, bevacizumab; CBDCA, carboplatin 175 mg/m² every week for 4 weeks repeated after 2 weeks; CCNU, lomustine; CT, chemotherapy; GBM, glioblastoma; GKS, gamma knife surgery; IFN, interferon; IFXRT, involved-field radiation therapy; Iri, irinotecan; i.t., intrathecal; i.v., intravenous; KPS, Karnofsky performance status; LGG, low grade glioma; LMS, leptomeningeal spread; MTX, methotrexate; NA, not available; OS, overall survival; PCB, procarbazine; PD, progressive disease; RT, radiotherapy; Thio, thiotepa; TMZ, temozolomide; VP16, etoposide.

Some molecular alterations have been also suggested as risk factors of LMS [85]. Gain of 1p36 [105], *PTEN* mutation [102, 106], and *PIK3CA* mutations [107] seem to predispose to meningeal seeding [102, 105, 106]. O6-methylguanine-DNA methyltransferase promoter methylation was also proposed as a risk factor by isolated studies [65, 108]. The suspected mechanisms is increased survival in patients with *MGMT* promoter methylation GBM, giving time for tumor

cells to reach CSF [65]. This was not confirmed by larger studies [11, 109], and to date, no molecular signature has been validated as risk factor of LMS in high-grade glioma.

Antiangiogenic therapies (VEGF and COX2 inhibitors) have been suggested as promoters of distant recurrence including LMS [44, 48], but available data are conflicting. Further studies are needed [1, 49, 50, 110].

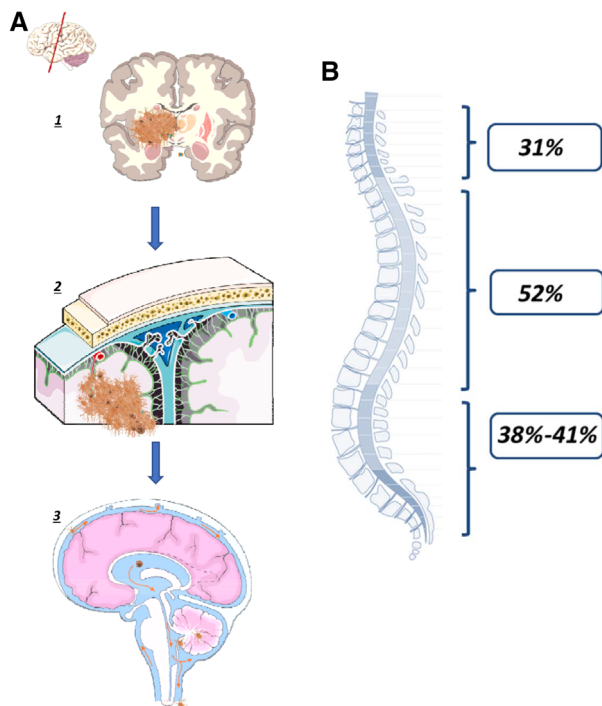


Figure 2. Leptomeningeal spread (LMS) in glioblastoma: routes of migration and spatial distribution of spinal LMS. **(A):** Routes of migration of glioblastoma cells from initial tumor site to meningeal spaces. **(1, 2):** Migration of glioblastoma (GBM) cells from the initial tumor site along brain vessels to subpial and subarachnoid spaces. **(3):** GBM cells circulating via the cerebrospinal fluid. **(B):** Distribution of leptomeningeal and spinal dissemination of intracranial glioblastoma.

DIAGNOSTIC APPROACH

Imaging

Currently, the standard examination for LMS diagnosis is contrast MRI with a sensitivity reported between 90% and 100% for brain [1, 6, 11, 99, 111–114] and between 56% and 95% for spinal LMS in symptomatic patients [1, 6, 11, 114]. Radiological screening of the neuraxis is required in patients with GBM and suspected LMS symptoms [31, 71, 111].

However, the benefit of neuraxis screening for patients with GBM without LMS symptoms remains unclear. This could be considered because the presentation can be asymptomatic and LMS can occur with stable disease at initial tumor site, particularly in subgroups at high risk of LMS [1, 29, 56, 59, 63, 103, 111]. Exceptional cases of asymptomatic LMS-like leptomeningeal enhancement on MRI were reported in the setting of radio-induced pseudoprogression [115].

Typically, LMS appears on MRI as linear and/or nodular foci with high signal intensity on T2 weighted images, low signal intensity on T1 weighted images, and enhanced after gadolinium injection [111]. An MRI LMS pattern was proposed using enhancement characteristics: (a) nodular, type Ia (Fig. 3); (b) diffuse, type Ib (Fig. 4) in the subarachnoid space [18, 34]; and (c) subependymal dissemination, type II (Figs. 3, 5) is also described regardless CSF cytology status

[34]. Mixed pattern is also possible (Fig. 5) [1, 34]. Distribution of LMS varies, commonly involving the anterior parts of brain stem and cranial nerves [101]. Still, the expanded use of antiangiogenic agents seems to modify this pattern making it more difficult to distinguish, in these cases a potential interest of contrast-enhanced fluid-attenuated inversion-recovery sequences can be discussed [34, 55].

In intracranial LMS, brain MRI can show multiple aspects: (a) nodular enhancement, 38% (subarachnoid or ventricular; Fig. 4) and (b) pial enhancement, 47% (focal or diffuse) [1, 11, 34]. Nerve roots enhancement can be seen in some cases (57%) as well as cranial nerve infiltration (11%–19%) [1, 34, 78]. Exceptional presentation mimicking chronic subdural hematoma or empyema has been reported [116, 117].

Spinal LMS has been reported to be more frequently in lower thoracic, upper lumbar (most often posterior) [36, 101], lumbosacral regions, cauda equina, and dural sac [36]. Thirty-one percent of lesions are described on the cervical level, 52% on the thoracic level, and 41% at the lumbar level (Fig. 2B) [1, 34, 101, 111]. Cauda equina and conus medullaris were involved in up to 38% of cases [1, 111].

Intraoperative detection of LMS using 5-aminolevulinic acid was reported as useful in anaplastic astrocytoma (histone K27M mutated) [9], but its benefit is inconsistent [66]. Nuclear imaging detecting hypermetabolic foci using ^{18}F -fluorodeoxyglucose [22, 23] or translocator protein with ^{18}F -flutriclamide [118, 119] can be helpful.

CSF Study

CSF analysis is often negative for detection of tumor cells; only 25%–45% are positive after a first assay [1, 11, 30, 65]. Repeated lumbar puncture increases the diagnostic sensitivity to 86% with three consecutive lumbar punctures [65, 71, 78] and to 93% with more than three lumbar punctures [6]. Nevertheless, even in cases of radiologically confirmed LMS, CSF cytological results were positive in only 4%–75% of cases, making an abnormal neuropathological CSF study sufficient but not necessary for diagnosis of LMS in gliomas [1, 6, 11, 28, 65, 85]. Indirect aspects can be observed as high intracranial pressure (>15 cm H_2O), high protein level (>50 – 100 mg/dL) with or without low glucose, and high lactate with an acellular aspect [15, 85, 120], although a mild pleocytosis with presence of macrophages has been described [94].

On cytological examination, GBM cells were noted most often to be singly dispersed in the CSF (Fig. 2A). The main challenge is their distinction from monocytes (Fig. 6) [18].

The input of liquid biopsies in diagnosis and monitoring of LMS in patients with GBM has been explored with increasing interest over the last years [121–123]. Collecting and analyzing tumor components floating in CSF (i.e., circulating tumor cells [CTCs], cell-free tumor DNA RNAs [circulating tumor RNA, microRNA, and exosomes]) may help noninvasive diagnosis of central nervous system tumors and heighten the sensitivity of LMS detection [121, 122, 124]. CTCs and ctDNA seem to be of clinical interest [125]. In systemic malignancies CSF CTC assay has a reported sensitivity between 81% and 100% and a specificity of 85%–97%. However, for

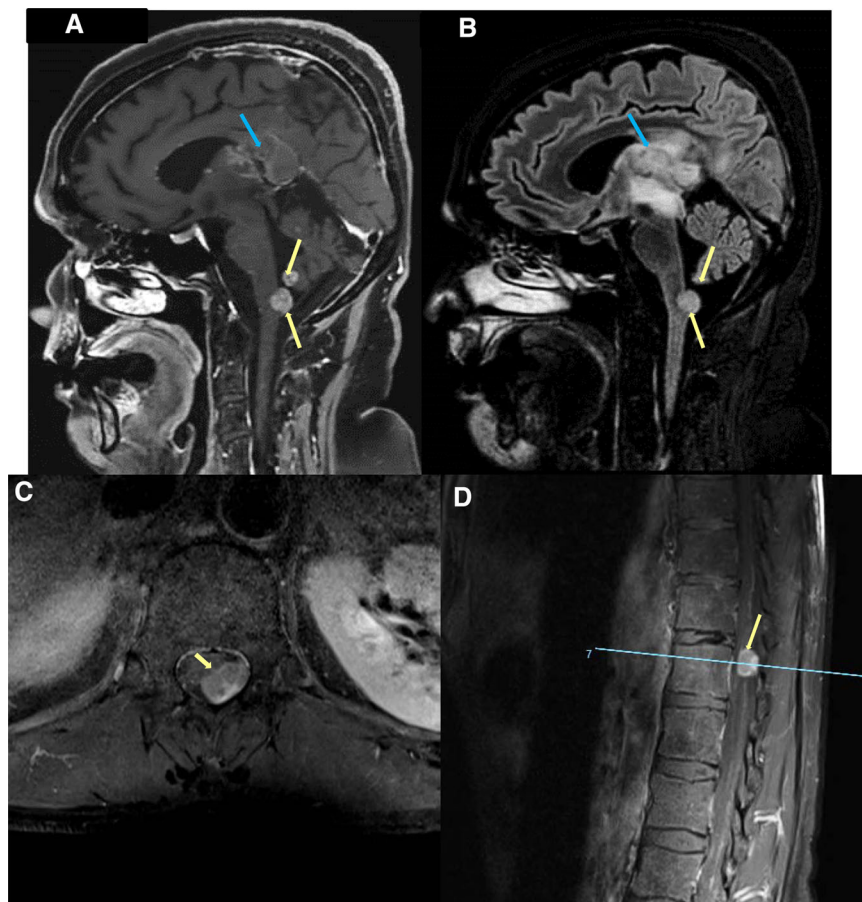


Figure 3. Nodular leptomeningeal spread in glioblastoma. (A, B): Subependymal. (C, D): Spinal. Blue arrow indicates initial location; yellow arrow indicates nodular leptomeningeal spread.

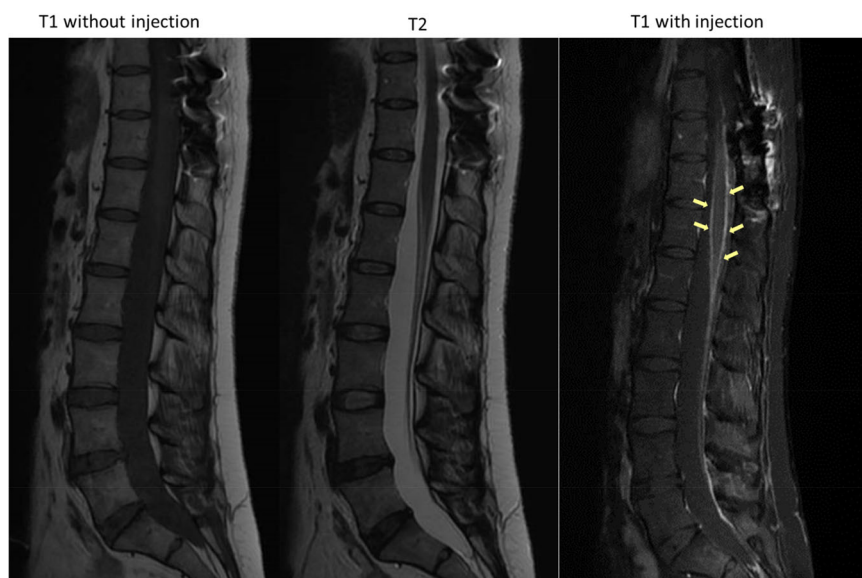


Figure 4. Linear (diffuse) leptomeningeal spread in glioblastoma.

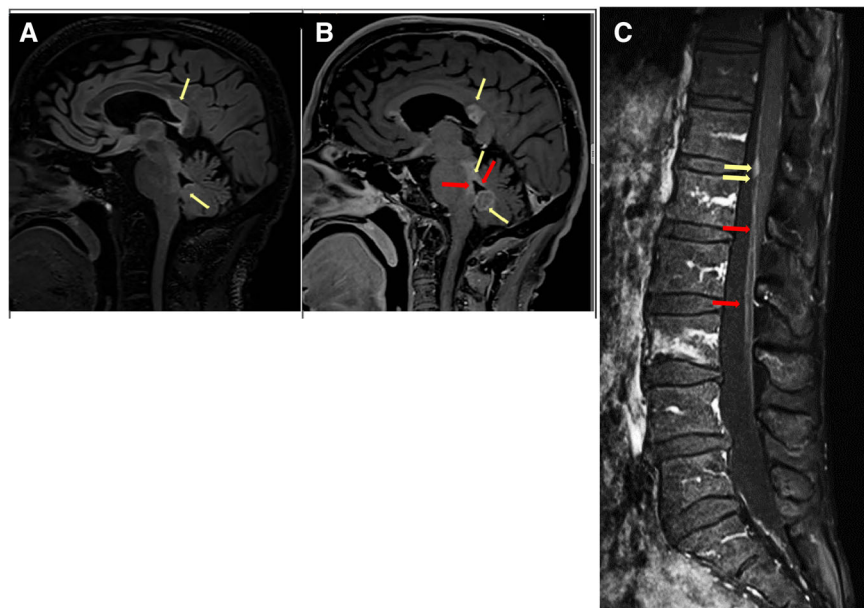


Figure 5. Mixed leptomeningeal spread in glioblastoma. **(A, B):** Subependymal. **(C):** Spinal. Yellow arrows indicate nodular aspects; red arrows indicate linear aspects.

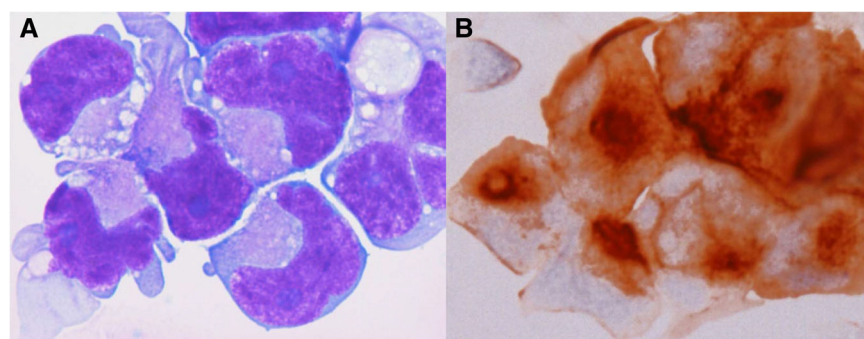


Figure 6. Cytopathological aspects of leptomeningeal spread in glioblastoma. **(A):** Cerebrospinal fluid obtained from lumbar puncture was studied by cytocentrifugation and May-Grünwald-Giemsa staining. Microscopic examination showed large tumor cells with marked atypia (high nucleocytoplasmic ratio, irregular nuclear borders, prominent nucleoli, basophilic cytoplasm). **(B):** GFAP immunostaining (brown signal) showed cytoplasmic positivity confirming the glial lineage of the tumor cells.

nonepithelial malignancies such as GBM, the appropriate detection technique needs to be established [121, 125].

As for the CSF ctDNA, analysis can be particularly useful for detection of clonal mutations (*BRAF*^{V600E}, *IDH1*, *IDH2*, *TERT* promoter, *ATRX* and *TP53* mutations, *EGFR* amplification) [23, 121, 122, 126]. Of note, although there is a clear correlation between CSF ctDNA and survival, the CSF detection of ctDNA does not systematically mean LMS; its clinical value in this context remains to be established [121].

Therapeutic Approach

In most cases, LMS in patients with glioma is considered an untreatable end stage complication of the disease [34]. There is no consensus or standard of care regarding treatments [81]. Multiple treatment modalities, such as intrathecal

chemotherapeutics and radiation therapy, seem to have improved median survival from 4–6 weeks to 3–6 months in high-grade gliomas [127]. Survival of patients with LMS and GBM in studies is reported at 0.2–9.7 months with a mean of 4.7 months [1, 28, 128].

Progression of the disease or treatment-related complications (such as hemorrhage [129] and infections [20, 33] after intrathecal administered treatment or ventriculoperitoneal shunting [20, 130, 131]) may sometimes contribute to the fatal outcome [82, 129].

Surgery

Because of the multifocal character of LMS, a surgical approach is not suitable [87]. Surgical resection of compressive nodular focal leptomeningeal lesions may provide symptomatic benefit without affecting survival [9, 68, 83]. Another use for surgery in LMS is placement of a ventriculo-peritoneal (VP) shunt in

Table 2. Molecular targeted therapies for leptomeningeal spread in patients with glioblastoma

Study	n	Age (years), sex	Histology	Latency, months	Location LMS	Targeted therapy	CSF	PFS (FD)	OS, months
Woo et al. 2019 [23]	1	22, F	Epithelioid: GBM <i>BRAF</i> ^{V600E}	0	Intracranial and spinal	First line: Dabra + Trame Second line: Nivolumab Spinal RT	Y NGS Y HML 17.1/mb Cell-free DNA	3	7
	1	23, M	Epithelioid: GBM <i>BRAF</i> ^{V600E}	1	Intracranial NA for spinal	First line: Vemu + Cobi Second line: TMZ CCRT + Vemu + Palbo	Cell-free DNA in CSF <i>BRAF</i> ^{V600E} 35.7%	1.5 2	7.5
Abadal et al. 2017 [24]	1	34, F	Nonepithelioid GBM <i>BRAF</i> ^{V600E}	11	Cranial and spinal	Prior to LMS: CCRT and adjuvant TMZ and switch to bevacizumab alone First recurrence with LMS: Vemu	NA	>11	>22
Burger et al. 2017 [25]	1	25, M	Nonepithelioid: GBM <i>BRAF</i> ^{V600E}	9	Cranial	First line, prior to LMS TMZ CCRT and adjuvant TMZ Second line post LMS development: lomustin Third line: Dabra	NA	>3	NA
Kanemaru et al. 2019 [26]	1	57, M	Epithelioid: GBM <i>BRAF</i> ^{V600E}	<2	Cranial and spinal	First line: TMZ CCRT Second line: Dabra + Trame + spinal RT	NA	NA	8 mo
Leaver et al. 2016 [76]	1	26, M	Epithelioid GBM <i>BRAF</i> ^{V600E}	1	Intracranial LMS and extra-axial (lung)	Vemu	NA	1	<2

Abbreviations: CCRT, concomitant chemoradiotherapy; CSF, cerebrospinal fluid; Cobi, cobimetinib; Dabra, dabrafenib; F, female; FD, follow-up duration; GBM, glioblastoma; HML, high mutational load; LMS, leptomeningeal spread; M, male; NA, not available; NGS, next-generation sequencing; OS, overall survival; RT, radiotherapy; Palbo, palbociclib; PFS, progression-free survival; TMZ, temozolomide; Trame, trametinib; Vemu, vemurafenib; Y, yes.

case of hydrocephalus [11, 14, 20, 72, 130, 132]. This seems to be necessary in up 20%–30% of patients [11]. The main complications are shunt occlusion caused by high fibrinogen CSF concentration [131, 133], VP valve malfunction [133], hemorrhage, and meningitis [20, 130, 133] as well as extracranial dissemination in peritoneal cavity [111, 133]. The latter is exceedingly rare, although postmortem diagnosis in asymptomatic patients is possible [111, 133]. In case of shunt occlusion, the use of urokinase can be considered [131], and careful monitoring should be ensured [20, 130].

Radiotherapy

Palliative radiation therapy is the most commonly used treatment modality. Doses between 20 to 40 Gy are usually delivered allowing a good symptomatic control, especially for pain relief [27, 68, 87, 31, 134], compressive symptomatology [83, 87], or intractable vomiting caused by seeding to fourth ventricle [81]. Although focal LMS from systemic cancers is sometimes treated by stereotactic radiosurgery, its use in GBM LMS is rarely reported [1, 6, 60]. The clinical benefit is limited in terms of neurological deficit recovery or survival when administered alone [27, 33, 68, 84, 87, 135], and it improves slightly when added to surgery [27, 68, 69]. Isolated

trials of radiolabeled monoclonal antibodies failed to significantly improve the survival of patients with LMS [136].

Pharmacological Treatment

Multiple chemotherapeutic regimens have been investigated: (a) temozolomide alone or combined with carmustine [7] or lomustine [55], (b) thiotepa alone [57, 58] or combined with procarbazine [20, 58, 64], (c) methotrexate [6, 15, 20, 57, 137], (d) cytarabine [19, 57, 128, 138, 139], (e) topotecan or irinotecan [15, 140, 141], and (f) platinum-based agents with or without etoposide [56, 74]. Drug administration was either oral [7], intravenous [1, 6, 11, 15, 64, 142] intrathecal via Ommaya reservoir or lumbar puncture [6, 11, 19, 21, 57, 58, 138, 140, 141] or subcutaneous port [137], or combined [1, 6, 7, 11, 20, 110].

Antiangiogenic drugs (e.g., bevacizumab) alone [1, 44, 117, 142] or combined with cytotoxic agents (e.g., irinotecan) were used with inconsistent clinical benefit [15, 55, 64, 85, 110, 134, 143]. Concurrent radiochemotherapy can be proposed in selected cases, eventually in association with antiangiogenic agents [15, 31, 55, 134].

Targeted therapy can be advised in selected cases (Table 2); for example, the MAPK pathway inhibitors

Table 3. Early phase clinical trials for LMS

Study	n	Targeted tumors	Mean age, years	Histology	Prior treatments	LMS treatment	Administration	Response	Toxicity	Mean PFS, days	Mean OS, days
Brown et al. 1996 [136] Phase I	31	Glioma LMS	48	17 GBM (rest: other-grade glioma, pediatric glioma)	RT and CT × 13 No prior treatments × 4	¹³¹ I labeled 81C6 mAb (anti-tenascin)	i.t. (Ommaya/Rickham)	5 SD (clinical and radiological) 1 radiological PR 12 PD	41% Gr 3–4 neutropenia and thrombopenia	56	171 (5–393 +)
Gammon et al. 2006 [140] Phase I–II	11	Glioma LMS	57	6 GBM 5 other-grade glioma	CT ± gefitinib	Topotecan Added to systemic CT	i.t.	6 CSF clearance after first dose 2 after second dose 1 after the fifth	Mild meningeal irritation 2/11 Gr 2 rash Gr 1–2 fatigue	NA	NA
Chamberlain et al. 2003 [57] Phase II	18	Glioma LMS	52.5	8 GBM AA	RT and CT	Methotrexate	i.t.	PR 25%	Transient aseptic arachnoiditis Myelosuppression 22%	NA	90 days
Levin et al. 1989 [21] Phase I/II	1	Agnostic		2 GBM	CT	i.t. ACNU Systemic CT	i.t.	1 SD 1 month response followed by recurrence	Radiculopathy Fatigue Nausea, vomiting	30 SD in one patient	NA
Glantz et al. 1999 [139]	59	Agnostic	49	7 primary CNS tumors	NA	Methotrexate vs. Depocyt	i.t.	5/7 response for Depocyt 2/7 MTX	Hematological CNS infections	NA	NA

Abbreviations: × number of patients having received RT; AA, anaplastic astrocytoma; ACNU, nimustine; CNS, central nervous system; CSF, cerebrospinal fluid; CT, chemotherapy; GBM, glioblastoma; Gr, grade; i.t., intrathecal; LMS, leptomeningeal spread; mAb, monoclonal antibody; MTX, methotrexate; NA, Not available; PD, progressive disease; PR, partial response; RT, radiotherapy; SD, stable disease.

(i.e., BRAF and/or MEK inhibitor) can be considered in *BRAF*^{V600E} mutant GBM [23]. Dramatic clinical and radiological response were reported with a survival benefit from 1 to 11 months [23–25, 76]. This motivates to extensive molecular testing [23–25].

As the brain-blood barrier breakdown is low and given the potential resistance mechanism, combined therapy with anti-MEK should be considered from the start as it seems associated with longer survival [23, 26]. Radiotherapy can be discussed to increase survival while balancing the treatment benefit and its toxicity [144, 145]. Because of the rarity of druggable targets in GBM, this option is available for about 6% of patients with LMS GBM [11].

Immunotherapy

Immune checkpoint inhibitors were proposed in cases of high mutational load and with microsatellite instability, alone or in combination with molecular targeted therapies [23, 146]. Nevertheless, there is no clear evidence of their efficacy in LMS [6, 22, 85, 146]. The use of adoptive cell therapy seems to be of interest. The IL13R α2-targeted chimeric antigen receptor (CAR) T cells (with 4-1BB as costimulatory domain and tCD19 as a marker for transduction) had encouraging results with no high-grade therapy-related side effects when used in a LMS of *IDH* wild type, *MGMT* methylated GBM [22, 147]. After repeated intraventricular administration of IL13BBζ CAR T cells, a clinical and radiologic response was sustained up to 7.5 months [22]. Other constructs targeting EGFRvIII and HER2 having different costimulatory domains were explored, but their impact on LMS is not reported [148, 149]. However, the difficulty in finding an adequate target, the immunosuppressive microenvironment, and the consequent toxicities are the limitations of immunotherapy in GBM, including in patients with LMS [147].

Among other approaches, we count gene therapy using engineered mesenchymal stem cells transduced with herpes simplex virus–thymidine kinase gene followed by systemic ganciclovir in a rat experimental leptomeningeal glioma model that seems to have encouraging results [150] and oncolytic viruses tested in transgenic mice inoculated with GBM cells [151]. Intrathecal immunoconjugates have also been advocated [90, 152] as well as intratumoral/intrathecal targeted therapy [153].

The completed clinical trials (Table 3) explored the use of multiple intrathecal chemotherapies including topotecan, methotrexate, and cytarabine in LMS. Although the safety profile was satisfactory, none of them showed significant improvement of survival in patients with LMS [21, 57, 139, 140]. Of note, the ongoing disease-agnostic clinical trials (Table 4) allow inclusion of patients with LMS and GBM. Nonetheless, their severe neurological impairment and their poor prognosis limit their enrollment.

After the literature review, a management algorithm is proposed in Figure 7.

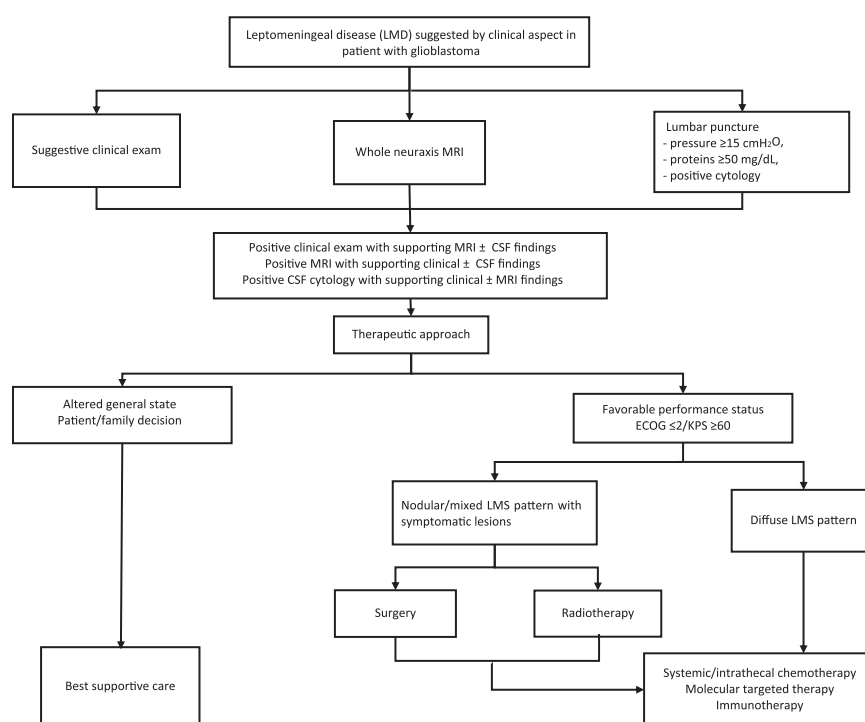
SURVIVAL

LMS in primary malignant central nervous system tumor implies more aggressive behavior and a worse prognosis.

Table 4. Ongoing clinical trials for LMS (as identified on clinicaltrials.gov)

Ongoing trial	Phase	Histology	Title	Drug
NCT03719768	Phase I	Agnostic	Avelumab with Radiotherapy in Patients with Leptomeningeal Disease	Avelumab and RT
NCT03091478	Phase II	Agnostic	Pembrolizumab in Leptomeningeal Disease	Pembrolizumab
NCT03423628	Phase I	GBM and GBM LMS	A Study to Assess the Safety and Tolerability of AZD1390 Given with Radiation Therapy in Patients with Brain Cancer	AZD 1390 RT
NCT00445965	Phase II	Agnostic	Iodine I 131 Monoclonal Antibody 3F8 in Treating Patients with Central Nervous System Cancer or Leptomeningeal Cancer	131I-3F8
NCT00089245	Phase I	AGNOSTIC	Radiolabeled Monoclonal Antibody Therapy in Treating Patients with Refractory, Recurrent, or Advanced CNS or Leptomeningeal Cancer	Iodine I 131 MOAB 8H9
NCT02939300	Phase II	agnostic	Ipilimumab and Nivolumab in Leptomeningeal Metastases	Ipilimumab, nivolumab

Abbreviations: CNS, central nervous system; GBM, glioblastoma; LMS, leptomeningeal spread; RT, radiotherapy.

**Figure 7.** Proposed algorithm for management leptomeningeal spread in glioblastoma.

Abbreviations: CSF, cerebrospinal fluid; ECOG, Eastern Cooperative Oncology Group performance status; KPS, Karnofsky performance status; LMD, leptomeningeal disease; LMS, leptomeningeal spread; MRI, magnetic resonance imaging.

Mean overall survival after diagnosis of treated LMS in high-grade gliomas is 4.94 months (2–9 months) [1, 6, 7, 27, 44, 60, 86, 142]. Exceptional overall survival up to 12 months was reported in cases with nodular LMS for which surgical resection was possible [83].

Among treated patients, the median overall survival was higher regardless chemotherapeutic regimen, but the bias of delivering more intensive treatments in patients in better performance status should be taken into account [1, 6, 7, 11, 58, 73, 138, 140]. Among studies, there seems to be a tendency of better survival for patients having received intrathecal chemotherapy (either Depocyt or thiotepa) with mean survival up to 10 months [20, 30]. A better

survival seems associated with antiangiogenic (6–7.6 months mean survival) [11, 55, 142] and molecular targeted therapy when appropriate [11, 24, 25]. Nevertheless, all these data need to be validated in prospective trials.

Despite significant efforts to standardize the response assessment in LMS, this has proven challenging [154], and it varies according to clinical trial outcome measures. The main criteria for assessing objective response in LMS treatments are the improvement of CSF cytology [139, 140] and radiological decrease of LMS extent [1, 6, 7, 11, 15].

Up to 50% of patients with LMS are treated only by best supportive care, and considering the symptom severity, we

need to underline importance of palliative care guidelines in LMS management [155].

PROGNOSTIC FACTORS

Although the reserved prognosis of LMS is well known, data on the prognostic factors are limited. The interval time from the initial glioma diagnosis to the LMS diagnosis is a potential prognostic factor [7] as well as Karnofsky performance status [30, 82]. Male patients seem to have shorter progression-free survival, although the impact on overall survival does not seem significant [30]. Of note, the extent of LMS does not seem to have a predictive value [1].

CONCLUSION

Data on LMS in patients with GBM remain scarce although it has become more common in neuro-oncology clinics. The main problems are the lack of reliable early diagnostic tools and consensual standard of care.

Based on our review of the literature, multimodal treatment of LMS, including surgery, radiotherapy, chemotherapy and/or best supportive care, is a suitable approach to be discussed during multidisciplinary brain tumor board.

Interestingly, given the advances in glioma therapeutics, including molecular targeted therapies and immunotherapies, the landscape of LMS treatment is evolving. However, investigation of these innovative treatments remains limited in the setting of LMS and needs further studies. Given the dismal prognosis

and increasing incidence of this GBM complication, identification of risk factors, biomarkers, and efficient therapeutic options in large prospective studies and clinical trials is warranted.

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